Applying Computational Modeling to Observe the Effect o E-4031 and Chromanol on Cardiomyocytes

Daria Shifrina, Bonnie Quach, David Christini

Introduction

Chromanol and E-4031 are prototypical drug blocks used to block potassium currents, effectively prolonging the repolarization stage of a cardiac action potential. E-4031 blocks I_{Kr} and Chromanol blocks I_{Ks}. Understanding the effect of Chromanol and E-4031 on electrical activity is essential to developing a better drug that will ultimately prevent heart failure. Chromanol and E-4031 cause arrhythmias by prolonging the cardiac action potential as a result of blocking the potassium channels. A prolonged action potential has been shown to elongate the QT interval, affecting the ability for the atria and ventricles to coordinate contraction and relaxation, thereby reducing blood pressure and flow.

Purpose/Hypothesis

We hypothesize that there is interplay between different potassium currents when one is affected. Since there is a strong correlation between mutations in potassium-encoding genes and cases of arrhythmias, we hypothesize that subduing I_{Kr} and I_{Ks} currents to mirror what some mutations do, will effect the duration of the action potential and the duration of the other potassium currents.

Methods

Using the computational model of an iPSC-derived ventricular cardiomyocyte (Paci et al., 2013), we will analyze the changes in the ionic currents I_{Kr} and I_{Ks}, as well as the overall effect on the action potential. This computational model allows us to adjust the numerous currents affecting the AP and implement drug blocks. The model was adjusted by increasing the conductance of I_{K1} to inhibit spontaneous activity and make action potential characteristics more “adult-like”. The model reflects the effect of the drugs by adjusting the conductance of the current. In the end, the action potential is derived from all of the ionic currents. Some currents also change to reflect the changes in the AP.

We begin by setting our simulation to last 200 seconds in order to reach steady-state. Then we set the stimulation frequency to 60 times per minute in order to more accurately mirror the behavior of a cardiac action potential, which fires without any external stimulus. We create 6 data sets to worth with: the first being the control, with no drug blocks. Then we simulated different concentrations of drug.
We generate results for the control, and then the different amounts of the drug blocks of E-4031: 30nM and 100nM, and the results for the different amounts of the drug block Chromanol: 30nM, 50nM, 70nM, and 90nM.

We graphed our data with time versus current generated for all of our data sets to observe any notable changes to the currents and APs produced throughout the duration of the simulation. To understand the data better, we focus on a specific time frame near the end of the simulation that is reflective of the trends in data preceding it.

Effect of E-4031

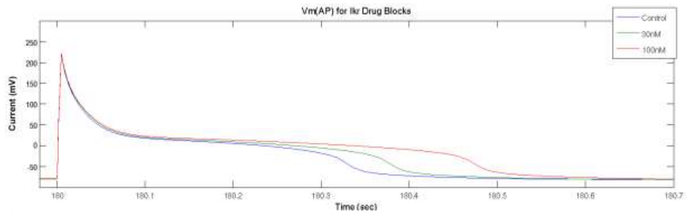

Fig. 1: As amount of E-4031 is increased, duration of AP increases from 400ms, to 500ms (30nM), to 600ms (100nM). Phase 3 takes significantly longer with drug block than with control.

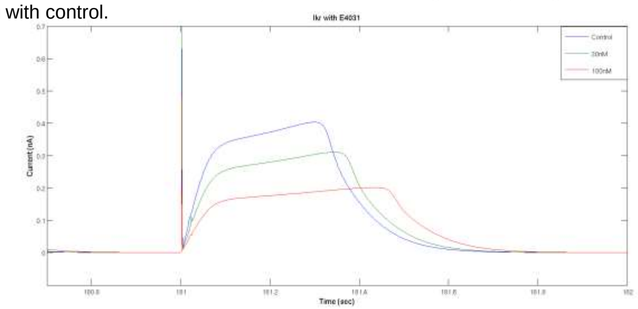

Fig. 2: As amount of E-4031 is increased, duration of the I_{Kr} current increases, and the current amount decreases. This causes the potassium channels to stay open longer and extends repolarization of the AP.

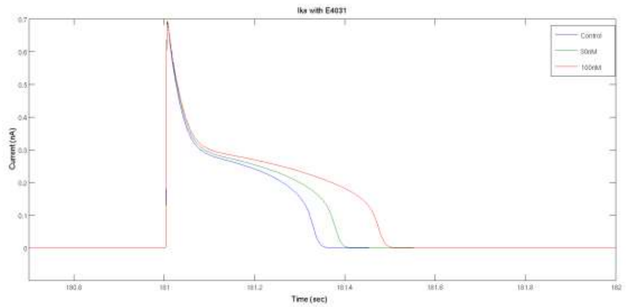

Fig. 3: As amount of E-4031 is increased, duration of the I_{Ks} current increases, and the current amount increases. This is a side effect of a longer AP, as the I_{Kr} channel remains open for longer during the repolarization period.

Effect of Chromanol

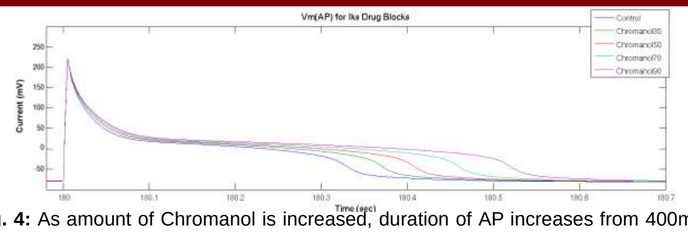

Fig. 4: As amount of Chromanol is increased, duration of AP increases from 400ms, to 450ms(Ch30), to 500ms(Ch50), to 600ms(Ch70), to 700ms(Ch90). Phase 3 takes significantly longer with drug block than with control, and effects are more prominent than with E-4031.

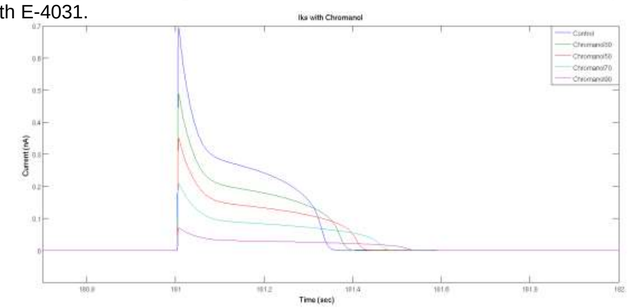

Fig. 5: As amount of Chromanol is increased, duration of the I_{Ks} current increases, and the current amount decreases. This causes the potassium channels to stay open longer and extends repolarization of the AP.

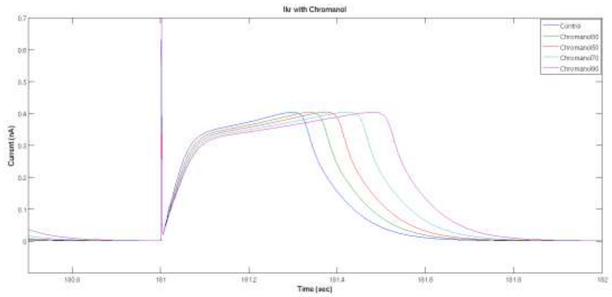

Fig. 6: As amount of Chromanol is increased, duration of the I_{Kr} current increases, and the current amount decreases. This is a side effect of a longer AP, as the I_{Kr} channel remains open for longer during the repolarization period.

Conclusions

Chromanol and E-4031 prolong the duration of the cardiac action potential in the ventricular cells by blocking the ionic currents I_{Kr} and I_{Ks} and extending their durations. A longer AP often prolongs the QT interval, which slows electrical depolarization and repolarization of the ventricles, causing an abnormal heart rate, known as arrhythmia.

Future Directions

-Effect of I_{Kr} and I_{Ks} on sodium-calcium currents and how that impacts the AP.
-Effect of the potassium currents on the atria and the relationships between the APs in the atria and then APs in the ventricles.
-Effect of I_{Ks} and I_{Kr} on the AP if the currents are increased rather than subdued.

NewYork-Presbyterian
Weill Cornell Medical Center